Induction of angiogenesis by smooth muscle cell-derived factor: possible role in neovascularization in atherosclerotic plaque.

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The development of atherosclerotic plaque is associated with neovascularization in the thickened intima and media of vascular walls. Neovascularization may have a role in the progression of atherosclerotic plaque as well as in the development of intraplaque hemorrhage. However, the mechanism and stimulus for neovascularization in atherosclerotic plaque are unknown. We postulated that smooth muscle cells (SMCs), a major cellular component in the vascular wall, might contribute to the induction of neovascularization in atherosclerotic plaque through the secretion of an angiogenic factor. We observed that endothelial cells (ECs) cultured on collagen gel with SMC-conditioned medium became spindle shaped, invaded the underlying collagen gel, and organized a capillary-like branching cord structure in the collagen gel. The conditioned medium also stimulated EC proliferation and increased the EC-associated plasminogen activator activity. The angiogenic factor in SMC-conditioned medium was retained in a heparin-Sepharose column and eluted with 0.9 M NaCl. Neutralizing anti-vascular endothelial growth factor (VEGF) antibody attenuated the angiogenic activity in the conditioned medium, including the induction of morphologic changes in ECs, mitogenic activity, and increased plasminogen activator activity associated with ECs. Immunoblotting analysis confirmed the secretion of VEGF from SMCs. These observations indicate that SMC may be responsible for the neovascularization in atherosclerotic plaque through the secretion of VEGF.

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Patients with combined hypercholesterolemia-hypertriglyceridemia show an increased monocyte-endothelial cell adhesion in vitro: triglyceride level as a major determinant.

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Hypercholesterolemia (HC) is one of the primary risk factors for atherosclerosis. Patients with familial hypercholesterolemia (FH) or combined hypercholesterolemia-hypertriglycerinemia (CHH) are at risk to develop premature atherosclerosis. Animal models have revealed that diet-induced HC in vivo leads to an increased adhesion of monocytes to the endothelium of the vessel wall. Changes in the monocytes, endothelial cells, or serum components may lead to the increased monocyte adhesion that results in atherosclerotic plaque formation. In the present study, we investigated the binding of the monocyte in an in vitro system. Incubation of freshly isolated monocytes from CHH patients with cultured human umbilical vein endothelial cells (HUVEC) gave a significant 60% increase in monocyte adhesion when compared with monocytes from healthy subjects. No such increase was observed using monocytes from nontreated FH patients. These data suggest that CHH results in in vivo alterations of the monocytes that lead to an increased in vitro adhesion to HUVEC, and that an increased level of plasma triglycerides is the major determinant, since HC alone does not induce this alteration.

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on long-term glucocorticoid therapy, but in individuals with diabetes mellitus, focal calcification may be accelerated and severe. It is much more common in diabetics with neuropathy, and sympathetic denervation of medial smooth muscle has been implicated in its cause.

Focal calcification also can produce the arteriosclerotic aortic valve in the elderly. Progressive calcium deposition occurs on the aortic surface of normal trileaflet aortic valves with age, resulting in a spectrum of clinical findings ranging from an innocent systolic murmur to severe calcific aortic stenosis (Chap. 201).

ARTERIOLOSCLEROSIS This disorder involves hyaline and degenerative changes affecting both the intima and media of smooth arteries and arterioles, particularly in the spleen, pancreas, adrenal, and kidney. In the kidney, but not necessarily elsewhere, arteriosclerosis is almost invariably associated with hypertension. Lesser degrees of sustained hypertension characteristically cause *hyalinization* of renal arterioles; more severe or malignant hypertension produces a typical *fibrous and elastic hyperplasia*, and even necrosis, of the media and intima.

ATHEROSCLEROSIS

LESIONS **Morbid anatomy** Atherosclerosis is a patchy nodular type of arteriosclerosis. The lesions are commonly classified as *early lesions* (*initial lesions* and *fatty streaks*), *intermediate lesions*, *fibrous plaques*, and *complicated lesions*.

Initial (fatty streak) and *intermediate lesions* are focal, small, and nonobstructive. Initial lesions may be detectable only chemically or microscopically, consist of lipid deposition in intimal macrophages (macrophage foam cells), and represent the first changes that have been found to evolve into lesions associated with clinical disease. Often found in children, they are located in atherosclerosis-susceptible regions of the arterial tree.

Fatty streaks are visible to the naked eye on the endothelial surface of the aorta and coronary arteries. They are still small and nonobstructive and contain a larger accumulation of lipid-filled smooth-muscle cells and macrophages (foam cells) and fibrous tissue in focal areas of the intima. They are stained distinctly by fat-soluble dyes but may be visible without staining as yellowish or whitish patches, streaks, or dots on the intimal surface. The lipid is mainly cholesterol oleate and is mainly intracellular.

Fatty streaks are visible in the aorta and coronary arteries of very young children and increase in the aorta at puberty. Whether or not these lesions progress to advanced lesions at particular sites depends largely on hemodynamic forces and the plasma levels of atherogenic lipoproteins. Those lesions that are prone to progression develop extracellular lipid and debris in the proteoglycan matrix so that lipid pools form among the layers of intimal smooth-muscle cells. At this stage, a single lipid core is not evident, cell death is not apparent, and cholesterol crystals are rarely found. These lesions are considered to be intermediate or preatheromatous, on the way to developing the lipid core characterizing the advanced lesion (atheroma or fibrous plaque).

Fibrous plaques are palpably elevated areas of intimal thickening and represent the most characteristic lesion of advancing atherosclerosis. These atheromatous lesions first appear in the abdominal aorta, coronary arteries, and carotid arteries in the third decade and increase progressively with age. They appear in men before women, in the aorta before the coronary arteries, and much later in the vertebral and intracranial cerebral arteries. Reasons for the difference in susceptibility of various segments of the arterial tree and the nonuniform distribution of lesions are not known. Typically, the fibrous plaque is firm, elevated, and dome-shaped, with an opaque glistening surface that bulges into the lumen. It consists of a central core of extracellular lipid (with cholesterol crystals) and necrotic cell debris ("gruel") covered by a fibromuscular layer or cap containing large numbers of smooth-muscle cells, macrophages, and collagen. Thus the plaque is much thicker than is normal intima. Although the lipid, like that of fatty streaks, is mainly cholesterol ester, the principal esterified fatty acid is linoleic rather than oleic, reflecting its largely extracellular distribution. Thus plaque cholesterol ester composition differs from fatty streaks but resembles plasma lipoproteins.

The *complicated lesion* is a calcified fibrous plaque containing various degrees of necrosis, thrombosis, and ulceration. These are the lesions frequently associated with symptoms. With increasing necrosis and accumulation of gruel, the arterial wall progressively weakens, and rupture of the intima can occur, causing aneurysm and hemorrhage. Arterial emboli can form when fragments of plaque dislodge into the lumen. Stenosis and impaired organ function result from gradual occlusion as plaques thicken and thrombi form.

Localization Although the term *generalized atherosclerosis* is commonly used clinically, lesions are actually irregularly distributed; different vessels are involved at different ages and to varying degrees. The abdominal aorta is involved earliest and most severely by atherosclerotic lesions, and it is the bellwether of lesions elsewhere. The aorta is usually most heavily involved at or near the orifices of its branches (particularly at the level of the coronary and intercostal arteries), in the aortic arch, and frequently at its bifurcation into the iliac arteries. There is more atherosclerosis in the lower than in the upper limbs. In the legs, the incidence decreases peripherally as the musculoelastic vessels give way to large muscular arteries and these become smaller vessels, such as the plantar or digital arteries. Plaques and thromboses are particularly common in the *femoral* artery, in Hunter's canal, and in the *popliteal* artery just above the knee joint. The *anterior* and *posterior tibial* arteries are often occluded together, but in different sites—the posterior where it rounds the internal malleolus and the anterior where it is superficial and becomes the dorsalis pedis artery. The peroneal artery, which is well embedded in muscle, often escapes when other major vessels are occluded, and it may be the main blood supply to the extremity (*peroneal leg*). Atherosclerosis in abdominal branches, except for the renal and mesenteric arteries, causes less difficulty than in coronary and cerebral vessels.

In the *coronary arteries*, raised lesions are most prominent in the main stems, the highest incidence being a short distance beyond the ostia. Atherosclerosis is nearly always found in the epicardial (extramural) portions of the vessels, while the intramural coronary arteries are spared. Coronary atherosclerosis is often diffuse. The degree to which the lumen is narrowed varies, but once the process is present, all the intima of the extramural portions of the vessel is usually involved. A single tiny plaque occluding an otherwise normal coronary artery is rare. Selective involvement of the coronary arteries may relate to the unique hemodynamic forces, unlike those of other major arteries, resulting from greater flow in diastole than systole. The implications of these flow patterns for atherogenesis are as yet unknown. Typical atheromatous fibrous plaques also develop in saphenous vein aortocoronary bypass grafts.

In the cervical and cerebral arteries the distribution of atherosclerosis is patchy, as it may be in other arteries. It first appears in the base of the brain in the carotid, basilar, and vertebral arteries. The proximal portion of the internal carotid artery in the neck is a site of special predilection. There is a concentration of lesions near bifurcations. Atherosclerosis in the *pulmonary artery* bears no relation to the severity of the disease in the aorta or other systemic arteries. There is some involvement in about half of adults over 50 years of age who have no reason to have pulmonary hypertension. Pulmonary hypertension per se, however, is associated with medial hypertrophy, intimal thickening, and great acceleration of atheroma formation.

THEORIES OF ATHEROGENESIS A generally accepted theory for the pathogenesis of atherosclerosis consistent with a variety of experimental evidence is the *reaction to injury* hypothesis. According to this idea, the endothelial cells lining the intima are exposed to repeated or continuing insults to their integrity. The injury to the endothelium may be subtle or gross, resulting in a loss of the ability of the cells to function normally and act as a permeability barrier. In the extreme, the cells may desquamate. Examples of types of

"injury" to the endothelium include metabolic injury, as in chronic hypercholesterolemia or homocysteinemia, mechanical stress associated with hypertension, and immunologic injury, as may be seen after cardiac or renal transplantation. Dysfunctional endothelial cells at susceptible sites in the arterial tree would lead to exposure of the subendothelial tissue to increased concentrations of plasma constituents. This may trigger a sequence of events including monocyte and platelet adherence, migration of monocytes into the intima to become macrophages, platelet aggregation and formation of microthrombi, and release of platelet and macrophage secretory products, including growth factors and cytokines (such as platelet-derived growth factor, interleukin 1, colony stimulating factors), in conjunction with plasma constituents, including lipoproteins and hormones such as insulin. This could stimulate the proliferation of intimal smooth-muscle cells at these sites of injury. These proliferating smooth-muscle cells would deposit a connective tissue matrix and accumulate lipid, a process that would be particularly enhanced with hyperlipidemia. Monocyte-derived macrophages also can accumulate lipids, some of which are in the form of lipid-protein complexes characteristic of oxidized lipoproteins. These cells are also capable of modifying lipoproteins in situ, favoring their uptake by scavenger receptors. Endothelial cells and macrophages can elaborate a chemoattractant protein that sustains accumulation of monocyte-derived macrophages.

Adherence of monocytes to altered endothelial cells and their migration into the arterial wall to become resident macrophages may be the earliest cellular abnormality in atherogenesis. Thus repeated or chronic injury could lead to a slowly progressing lesion involving a gradual increase in intimal smooth-muscle cells, macrophages, connective tissue, and lipid. Areas where the shearing stress on endothelial cells is increased, such as branch points or bifurcation of vessels, would be at greatest risk. As the lesions progress and the intima becomes thicker, blood flow over the sites will be altered and will potentially place the lining endothelial cells at even greater risk for further injury, leading to an inexorable cycle of events culminating in the complicated lesion. However, a single or a few injurious episodes may lead to a proliferative response that could regress, in contrast to continued or chronic injury. This hypothesis of reaction to injury thus is consistent with the known intimal thickening observed during normal aging, would explain how many of the etiologic factors implicated in atherogenesis might enhance lesion formation, might explain how inhibitors of platelet aggregation could interfere with lesion formation, and could elucidate how treatment targeted at risk-factor reduction can interrupt progression or even produce regression of atheromatous lesions.

Other theories of atherogenesis are not mutually exclusive. The *monoclonal hypothesis* suggests, on the basis of single isoenzyme types found in lesions, that the intimal proliferative lesions result from the multiplication of single, individual smooth-muscle cells, as do benign tumors. In this manner, mitogenic, and possibly mutagenic, factors that might stimulate smooth-muscle cell proliferation would act on single cells. Focal *clonal senescence* may explain how intrinsic aging processes contribute to atherosclerosis. According to this hypothesis, the intimal smooth-muscle cells that proliferate to form an atheroma are normally under feedback control by mitosis inhibitors formed by the smooth-muscle cells in the contiguous media, and this feedback control system tends to fail with age as these controlling cells die and are not adequately replaced. This is consistent with the observation that cultured human arterial medial smooth-muscle cells, like fibroblasts, show a decline in their ability to replicate as a function of donor age.

The *lysosomal theory* suggests that altered lysosomal function might contribute to atherogenesis. Since lysosomal enzymes can accomplish the generalized degradation of cellular components required for continuing renewal, this system has been implicated in cellular aging and the accumulation of lipofuscin or "age pigment." It has been suggested that increased deposition of cholesterol esters in arterial smooth-muscle cells may be related in part to a relative deficiency in the activity of lysosomal cholesterol ester hydrolase. Consonant with this idea, some patients with the rare cholesterol ester storage disease caused by a defect in lysosomal cholesterol ester hydrolase may have accelerated atherosclerosis. However, lipid droplets in foam cells are often cytoplasmic rather than lysosomal, and this theory is not now widely held.

RECOGNITION OF ATHEROSCLEROSIS Angiographic visualization of deformity in the lumen of a vessel remains the best presumptive test of silent atherosclerosis. Coronary angiography now permits visualization and assessment of arteries as small as 0.5 mm in diameter. Several sophisticated noninvasive techniques have been developed for demonstrating its presence. Doppler probes for measuring velocity and amount of blood flow have been used noninvasively and adapted to determine vessel outlines. Ultrasonic techniques are not yet clinically useful for detection of plaques in the coronary arteries.

Functional tests based on pathophysiologic or metabolic effects of a narrowed arterial lumen often give indirect clues. Assessment of electrocardiographic changes induced after standardized exercise is a relatively simple noninvasive aid to the diagnosis of coronary atherosclerosis with significant narrowing. Similarly, myocardial perfusion defects demonstrable with imaging techniques using radionuclides are usually attributable to atherosclerosis (Chap. 191). Digital plethysmography with exercise often unmasks significant atherosclerotic involvement of lower extremity arteries.

Radiographic demonstration of calcification in the location of arteries does not always indicate the presence of atherosclerosis. Although calcified coronary vessels usually indicate atherosclerosis, complete luminal obstruction may occur in the absence of any calcification. Calcification or beading of peripheral arteries is not correlated directly with atherosclerosis but more likely reflects medial sclerosis. Abnormalities in retinal arterioles evident on funduscopic examination are not well correlated with atherosclerosis in arteries. Thus, despite the availability of a variety of tests, detection of atherosclerosis usually awaits one of the clinical events attending a critical decrease of blood flow in an involved vessel. As yet there is no blood test for atherosclerosis. Knowledge of the prevalence and incidence of arteriosclerosis and most of the inferences concerning its causes are derived from tabulations of the appearance of its sequelae.

Ischemic heart disease (IHD), synonymous with *coronary heart disease* or *arteriosclerotic heart disease* (Chap. 203), is the most reliable indicator of atherosclerosis available today. Practically all patients with myocardial infarction, as defined by electrocardiographic and enzymatic changes, have coronary atherosclerosis. Rare exceptions are due to congenital anomalies of the coronary vessels, emboli, or ostial occlusion due to the other types of cardiac or vascular disease. Nontraumatic *sudden death* (Chap. 35) makes up a sizable portion of all deaths eventually certified as due to IHD. At autopsy, evidence of fresh myocardial infarction or of *coronary thrombosis* is usually absent. While ventricular fibrillation may have been due to sudden closure of a partially compromised vessel by a small thrombus or embolus or to *spasm*, none of these need have preceded a fatal arrhythmia. The majority of victims of sudden death have had a previous diagnosis of IHD; the number who had diabetes or hypertension is also significant. In epidemiologic studies of IHD, *angina pectoris* and electrocardiographic changes attributable to ischemia without infarction are considered "softer end points" and are treated separately.

Cerebrovascular disease (stroke) is a less reliable criterion for the presence of atherosclerosis. It includes *cerebral thrombosis* and *cerebral hemorrhage* (Chap. 368). Cerebral thrombosis, including infarction or softening without evidence of embolus, is usually due to atherosclerosis. On the other hand, cerebral hemorrhage is most often the result of congenital aneurysms or of vascular defects peculiar to hypertension and diabetes. Dissections of the aorta (Chap. 210), *peripheral vascular disease* (Chap. 211), thrombosis of other major vessels, and ischemic renal disease (Chap. 243) likewise are not used

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TITLE: Different effects of estrogen and progesterone on experimental **atherosclerosis** in female versus male rabbits. Quantification of cellular proliferation by bromodeoxyuridine.
AUTHOR: Hanke H; Hanke S; Finking G; Muhic-Lohrer A; Muck A O; Schmahl F W; Haasis R; Hombach V
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AB BACKGROUND: The aim of the present study was to compare the effect of estrogen and progesterone on the development of experimental **atherosclerosis** in female versus male rabbits to assess possible sex-specific differences. METHODS AND RESULTS: A total of 32 female and 32 male New Zealand White rabbits were ovariectomized or castrated. In addition to a 0.5% cholesterol diet, the rabbits received estradiol alone (1 mg/kg body wt [BW] per week), progesterone alone (25 mg/kg BW per week), or combined estradiol-progesterone in these dosages during 12 weeks. Ovariectomized female and castrated male rabbits served as control groups without hormone treatment. Before excision of the vessels, bromodeoxyuridine labeling was performed to determine the extent of cellular proliferation in the **atherosclerotic** lesions. The aortic arch was analyzed immunohistologically and morphometrically. An inhibitory effect of estrogen on intimal plaque size was found in female rabbits compared with the ovariectomized control group (0.7 +/- 0.5 versus 3.7 +/- 2.5 mm2, P < .002; proliferating cells, 3.1 +/- 1.8% versus 8.5 +/- 2.6%, P < .002). In combination with progesterone, however, estrogen was not able to reduce intimal plaque size or cellular proliferation. In contrast, estradiol in castrated male rabbits was not associated with an inhibitory effect on cellular proliferation or intimal thickening compared with controls (estrogen treatment, 7.6 +/- 2.1% proliferating cells and 2.8 +/- 1.0 mm2 neointima; control group, 7.2 +/- 2.1% cellular proliferation and 2.9 +/- 1.2 mm2 intimal thickening). CONCLUSIONS: Our data suggest that the atheroprotective effect of estrogen is probably due to a mechanism that is present in female rabbits only.

TI Different effects of estrogen and progesterone on experimental **atherosclerosis** in female versus male rabbits. Quantification of cellular proliferation by bromodeoxyuridine.

AB . . . The aim of the present study was to compare the effect of estrogen and progesterone on the development of experimental **atherosclerosis** in female versus male rabbits to assess possible sex-specific differences. METHODS AND RESULTS: A total of 32 female and 32. . . hormone treatment. Before excision of the vessels, bromodeoxyuridine labeling was performed to determine the extent of cellular proliferation in the **atherosclerotic** lesions. The aortic arch was analyzed immunohistologically and morphometrically. An inhibitory effect of estrogen on intimal plaque size was found. . .

CT Check Tags: Animal; Female; Male
17-Hydroxyprogesterone
*Arteriosclerosis: PA, pathology
*Bromodeoxyuridine: DU, diagnostic use
Cholesterol: BL, blood

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FILE SEGMENT: Literature
AN 1999-37731 DRUGU T E
AB Hormone replacement therapy (HRT) is reviewed with reference to menopause and cardiovascular risk, estrogen replacement therapy, progestogens and administration regimens. Following menopause, the risk of cardiovascular disease in women increases significantly. Studies to date suggest that estrogen based HRT decreases the incidence of cardiovascular disease in post-climacteric women due to its effects on cholesterol metabolism and deposition. Progestogens must be added to estrogen HRT in women with an intact uterus in order to prevent hyperplasia and carcinoma, however, the effects of progestogens on the cardiovascular system are still under evaluation. Novel estrogen-like cardioprotectives without the detrimental effects on breast and uterus are currently under investigation.

ABEX The estrogen deficiency associated with menopause significantly increases risk of coronary artery disease. Following menopause, body fat distribution in women changes from the periphery to a central or android distribution. A substantial number of studies have indicated that exogenous estrogen has cardioprotective effects particularly in women with recognized . coronary risk factors. Estrogens induce a decrease in total serum cholesterol levels, particularly HDL2 and a decrease in LDL cholesterol levels. Menopause is associated with changes in clotting factors such as fibrinogen, factor VII and PAI-1, which are reversed by exogenous estrogen administration. HRT has also demonstrated effects on the arterial wall which influence the development of **atherosclerosis**, in addition estradiol administration increases arterial flow velocity, decreases vascular resistance and decreases B.P. Progestogens such as **17-hydroxyprogesterone** are thought to enhance the cardioprotective effects of estrogens on the lipid profile. The effects of progestogens alone in women has not really been studied as it is unusual to administer them alone. In general progestogens are added to HRT in order to oppose the effects of estrogen on the uterus and breast tissue. (JL)

ABEX. . . are reversed by exogenous estrogen administration. HRT has also demonstrated effects on the arterial wall which influence the development of **atherosclerosis**, in addition estradiol administration increases arterial flow velocity, decreases vascular resistance and decreases B.P. Progestogens such as **17-hydroxyprogesterone** are thought to enhance the cardioprotective effects of estrogens on the lipid profile. The effects of progestogens alone in women. . .

CT **ATHEROSCLEROSIS** *TR; MYOCARD.INFARCT. *TR; HEART-FAILURE *TR; THROMBOSIS *TR; VASCULAR-DISEASE *TR; ARTERIOSCLEROSIS *TR; CARDIOPATHY *TR; CORONARY-DISEASE *TR; CARDIOPATHY *TR; CASES *FT; IN-VIVO. . .

CT **ATHEROSCLEROSIS** *TR; MYOCARD.INFARCT. *TR; HEART-FAILURE *TR; THROMBOSIS *TR; VASCULAR-DISEASE *TR; ARTERIOSCLEROSIS *TR; CARDIOPATHY *TR; CORONARY-DISEASE *TR; CARDIOPATHY *TR; CASES *FT; IN-VIVO. . .

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AUTHOR: Chae C.U.; Ridker P.M.; Manson J.-A.E.
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LANGUAGE: English
SUMMARY LANGUAGE: English
AB Cardiovascular disease is the leading cause of mortality in postmenopausal women in developed countries. A possible cardioprotective role of hormone replacement therapy (HRT) is suggested by epidemiologic studies of HRT and reduced risk of coronary heart disease, as well as by randomized trials of HRT and lipid subfractions. Estrogen has beneficial effects on the lipid profile, raising high-density lipoprotein cholesterol levels and reducing low-density lipoprotein cholesterol levels each by approximately 10%. Other possible biologic mechanisms include beneficial effects on vascular function, oxidative status, endothelial-dependent vasodilation, intimal hyperplasia and insulin sensitivity. Estrogen's net effects on coagulation and fibrinolysis are less clear. Estrogen replacement therapy is associated with decreased **atherosclerosis** in several animal models. However, most of the available data on HRT derive from observational studies or small randomized trials assessing biologic intermediates rather than clinical events. Further research, including large-scale randomized clinical trials, are required to evaluate definitively the role of estrogen replacement therapy, especially given uncertainties about the effects of combined estrogen-progestin therapy and the balance of benefits and risks of this common intervention in postmenopausal women.
AB . . . and insulin sensitivity. Estrogen's net effects on coagulation and fibrinolysis are less clear. Estrogen replacement therapy is associated with decreased **atherosclerosis** in several animal models. However, most of the available data on HRT derive from observational studies or small randomized trials. . .
CT Medical Descriptors:
*estrogen therapy
*hormone substitution
*ischemic heart disease: PC, prevention
*ischemic heart disease: DT, drug therapy
*ischemic heart disease: EP, epidemiology
*postmenopause
antioxidant activity
atherosclerosis: PC, prevention
cardiovascular risk
conference paper
estrogen deficiency: DT, drug therapy
female
fibrinolysis
heart protection

hemostasis
hormonal regulation
human
lipid blood level
lipid metabolism
lipoprotein blood level
oral drug administration
priority journal
risk benefit analysis
secondary. . .

DNA: BI, biosynthesis
Estradiol: BL, blood
Estradiol: PD, pharmacology
. . .
RN 50-28-2 (Estradiol); 57-83-0 (Progesterone); 57-88-5 (Cholesterol); 59-14-3 (Bromodeoxyuridine); **68-96-2 (17-Hydroxyprogesterone)**; 9007-49-2 (DNA)